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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/755,747
Filing Date: January 05, 2001
Appellant(s): BROOKES, ANTHONY J.

Joseph T. Leone
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 8, 2005.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of invention contained in the brief is deficient because the summary states "The single stranded sample DNA is immoblized [sic] within a monolayer on a solid surface. Spec: 2/8-20 and Spec: 11, 9-10." This statement is not correct. A review of the specification at page 2, lines 8-20, finds that the specification makes no mention of a monolayer. A review of the specification at page 11, lines 9-10, shows that the specification states "The current binding surface format used is a 96 well microtitre plate that has been coated with steptavidin (available from various manufacturers)." Again, this sentence makes no mention of a monolayer. Consequently, the summary incorrectly states an element which is certainly not

expressly present in the specification, and about which there is significant argument as to whether the element is inherently present.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal in the brief is correct, though appellant's characterizations regarding the examination are not correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,174,670	Wittwer	1-2001
6,048,690	Heller	4-2000
5,789,167	Konrad	8-1998

Stimpson et al. "Real-time detection of DNA hybridization and melting on oligonucleotide arrays by using optical wave guides" Proc. Natl. Acad. Sci., vol 92 (July 1995), pp. 6379-6383.

Jordan et al. "Surface Plasmon Resonance Imaging Measurements of DNA Hybridization Adsorption and Streptavidin/DNA Multilayer Formation at chemically Modified Gold Surfaces" Anal. Chem., vol. 69 (1997), pp. 4939-4947.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112

Claims 1-5, 7-18, 20-31, 33-44, 46-52, and 67-76 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes " If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

The amendment to include the term "monolayer" is new matter. The specification of the instant application was wordsearched, both by an optical character recognition of the specification in the computer version of the application as well as by a word search of the published application. The word "monolayer" as well as the broader term "layer" were both searched (including plurals) and no basis was found for these terms. The response confines itself to the bare statement that "no new matter has been added by the amendments or new claims (see page 14 of response)" but no specific support for the term "monolayer" is identified in the response. Therefore, in the absence of any identified support for the term, the claims are rejected as containing new matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-71, 73, 74, and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stimpson et al (Proc. Natl. Acad. Sci. (1995) 92:6379-6383) in view of Wittwer (U.S. Patent 6,174,670).

Stimpson teaches a method of detecting DNA variation by monitoring the formation or dissociation of a of a complex (see abstract which states that "single base discrimination is facile") consisting of:

(a) a single strand of a DNA sequence (here the 15 mer oligonucleotide are attached to a glass solid support which is a monolayer of the nucleic acids, since each is directly attached to the glass support itself and not some three dimensional structure; see page 6380, column 1, for example),

(b) an oligonucleotide specific for the single stranded DNA sequence specific for one allele of the variation and capable of hybridizing to the single strand (a) to form a duplex (see the biotinylated complementary sequences, table 1 and page 6380-81, subheading "Hybridization and staining for wave guide")

(c) a marker detection of the duplex structure of (a) plus (b) which forms a complex with the said duplex (here the selenium label, see page 6381, figure 1, for example),

which method comprises:

(1) steadily and progressively adjusting the temperature by 1°C increments (see figure 3, page 6382, where melting curves were made by increasing temperature incrementally),

(2) continually measuring an output signal indicative of the duplex formed from the strand (a) and probe (b) (see page 6382, figure 3) and

(3) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page 6383, table 3, where the temperature at which the single base mismatch changes the signal).

Stimpson further teaches formation of two or more complexes, each with a probe specific for a different allele of the variation, and observing their respective denaturing or annealing conditions to distinguish alleles of the variation (see page 6382, figure 3, where two oligos, 23B and 24B are simultaneously tested).

Stimpson does not teach the use of a marker which is duplex specific in the analysis.

Wittwer et al teaches a method of detecting DNA variation by monitoring the formation or dissociation of a complex (abstract) consisting of:

(a) a single strand of a DNA sequence (here denatured genomic DNA (column 9, line 21) and/or denatured amplified PCR products, including an 81 basepair cystic

fibrosis gene product (column 40, lines 58-67)) as well as many longer PCR products such as the 536 base pair b-globin sequence (column 47, line 24),

(b) an oligonucleotide specific for the single stranded DNA sequence (here either the primers used in PCR (column 41, lines 1-20) or pairs of fluorescently labeled oligonucleotide probes (column 9, lines 27-37)),

(c) a marker specific for the duplex structure of (a) plus (b) which forms a complex with the said duplex and reacts uniquely when interacting within the duplex (here either SYBR green, (see column 40, line 65) or the fluorescence resonance energy transfer pair of labels, which differentially fluoresce when in duplex or single stranded states (column 9, lines 27-37)),

which method comprises:

(1) "monitoring fluorescence while changing temperature at a rate of 0.1 degree C/second."(see column 15, lines 25-26).

(2) continually measuring an output signal indicative of interaction of the marker with duplex formed from the strand (a) and probe (b) (see column 9, lines 50-55 or column 41, lines 14-17 and figure 43) and

(3) recording the conditions at which a change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a) (see page column 9, lines 55-59 or column 41, lines 14-17 and figure 43).

Column 14 details a similar assay for differentiating the Factor V Leiden mutation. Column 46 teaches the use of two or more complexes of the kind defined,

each with a probe specific for a different allele of the mutation which multiple detection probes are distinguished by the different melting peaks (see column 46, lines 49-61). Wittwer further teaches measurement of the annealing based upon the first or second derivatives of the fluorescent melting curves (column 12 and columns 23-26) and expressly discusses measurement of the second order rate constant (see column 12).

Wittwer expressly teaches with regard to claims 67-70 that "The melting curves are easiest to visualize by plotting the negative derivative of fluorescence with respect to temperature vs temperature (-dF/dT vs T) (column 45, lines 10-14)". Thus, with regard to the negative derivative of the fluorescent measurement, Wittwer is teaching determining the presence of a peak. Wittwer is clearly showing the presence of peaks in figure 46 B, where the homozygous and heterozygous (termed match and mismatch in the claim) are separately identified using the negative derivative data analysis method.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the markers of Wittwer in the mutation detection method of Stimpson since Wittwer states "SYBR™ Green I is a preferred double strand specific dye for fluorescence monitoring of PCR, primarily because of superior sensitivity, arising from greater discrimination between double stranded and single stranded nucleic acid. SYBR™ Green I can be used in any amplification and is inexpensive. In addition, product specificity can be obtained by analysis of melting curves, as will be described momentarily (column 23, lines 9-16)". Thus, an ordinary practitioner would have been motivated to use SYBR™ Green I in the melting curve

analytical method of Stimpson since Wittwer teaches that this intercalator is superior in sensitivity, is useful in the particular assay employed by Stimpson since the waveguides would detect the fluorescent label and is inexpensive.

Claims 1-5, 7, 8, 10-18, 20, 21, 23-31, 33, 34, 36-44, 46, 47, 49-52 and 67-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stimpson et al (Proc. Natl. Acad. Sci. (1995) 92:6379-6383) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Heller et al (U.S. Patent 6,048,690).

Stimpson in view of Wittwer teach the limitations of claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-71, 73, 74, and 76 as discussed above. Stimpson in view of Wittwer do not teach immobilization of the oligonucleotide using biotin-streptavidin.

Heller teaches immobilization of oligonucleotides to arrays using biotin-streptavidin for nucleic acid detection assays (column 16, lines 62-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the method of Heller in the detection method of Stimpson in view of Wittwer since Heller states "In this example, the first probe (a capture/quencher probe sequence) has two terminal functional groups, a 5'-terminal biotin group which allows the probe to be immobilized to the surface (permeation layer) of a microlocation test site on an active DNA chip or other hybridization device." (column 16, lines 62-67). An ordinary practitioner would have been motivated to use the biotin capture method in order to permit immobilization of probes to desired microlocations of DNA chips for the analytical method. Also, an ordinary practitioner

would be motivated to select a known equivalent of the method of Stimpson for attachment of the nucleic acids to the array as Stimpson teaches biotin capture methods (see page 6380, column 2).

Claims 1-6, 8-19, 21-32, 34-45, 47-52, 67-71, 73, 74 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stimpson et al (Proc. Natl. Acad. Sci. (1995) 92:6379-6383) in view of Wittwer (U.S. Patent 6,174,670) and further in view of Konrad et al (U.S. Patent 5,789,167).

Stimpson in view of Wittwer teach the limitations of claims 1-5, 8, 10-18, 21, 23-31, 34, 36-44, 47, 49-52, 67-71, 73, 74, and 76 as discussed above. Stimpson in view of Wittwer do not teach the use of Hepes buffer in hybridization.

Konrad teaches that " The conditions for hybridization of oligonucleotide sequences are well known. Generally, the hybridization step is either performed in a buffered aqueous salt solution at high temperature or in the presence of formamide at lower temperature. The aqueous, high temperature procedure is typically carried out in a Tris buffer, such as 0.3M NaCl, 20 mM Tris -HCl, pH 6.8, at 67.degree. C. Other buffering systems such as hepes or glycine-NaOH and potassium phosphate buffers can be used. (column 14, lines 59-67)".

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to utilize the Hepes buffer of Konrad in the detection method of Stimpson in view of Wittwer since Konrad expressly teaches that Hepes buffer is an equivalent buffer for use in hybridization reactions.

(10) Response to Argument

Issues

1. Is the amended claim term "monolayer", which lacks any support whatsoever in the specification, new matter?

2. Is there a prima facie case of obviousness for the claims?

Issue 1 – New Matter

Appellant argues that inclusion of the term "monolayer" into the claim, which is drawn to a method using only a monolayer of DNA strands, does not represent new matter based upon the inherent function theory of Kennecott Corp. v. Kyocera International Inc., 5 USPQ 2d 1194, 1197 (Fed. Cir. 1987). Appellant argues that there is evidence on the record which supports the arguments, including the Strohner declaration and manufacturer data sheets, and Appellant argues that the Jordan reference shows monolayers, not multilayers.

This new matter issue is significant, because without the term "monolayer" in the claim, the obviousness rejection of Drobyshev in view of Wittwer would be reinstated and applicable to the claims. This is particularly significant given Appellant's use of a term which has more than interpretation (as a simple "define:" will show in google), but for which Appellant would like to select a particular meaning.

(a) Appellant has misapplied the legal standard of Kennecott Corp to the present facts.

Appellant argues that the decision in Kennecott Corp. supports the position that the term "monolayer" is not new matter in the current specification. The first place to

look in order to determine whether a claim is new matter is to the specification itself. As noted throughout the prosecution, the term "monolayer" and indeed the term "layer" itself, do not appear anywhere in the current specification. Appellant correctly notes that ipsis verbis support is not, however required, to avoid new matter and that the Federal Circuit has permitted unrecited functions into the claim when "By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. Kennecott Corp. v. Kyocera International Inc, 5 USPQ2d 1194, 1197 (Fed. Cir. 1987).

To support the "inherent property" argument, the sole portions of the specification on which Appellant relies are the specification at page 11, lines 9-10, which states "The current binding surface format used is a 96 well microtitre plate that has been coated with steptavidin (available from various manufacturers)" and the teaching of a Boeringher plate at page 24. The claim, however, has no limitation to the specific plate used but is broadly drawn to any solid surface. The question that now arises is whether this statement is sufficient to disclose a device with an inherent property of having a "monolayer".

In Kennecott Corp., the claims were drawn to a sintered ceramic body with particular amounts of various materials. The issue was whether the description of the sintered ceramic body in the parent application inherently formed an equiaxed microstructure. Kyocera conceded that this structure was inherent and the Federal

Circuit relied upon this concession to find that the sintered ceramic body described in the specification of the Kennecott Corp. patent received benefit of priority to a parent application which did not discuss the limitation of equiaxed microstructure. The current case is easily distinguished from Kennecott Corp. on two grounds. First, as will be discussed supra, there is no concession that the "monolayer" is an inherent property of "single DNA strands which are bound to a solid surface (see claim 1)" based upon microtiter plates "available from various manufacturers (see specification at page 11, lines 9-10)."

Second, in Kennecott Corp., the specification of Kennecott Corp. itself provided the structure of the device which was found to have the inherent equiaxed microstructure. The sintered ceramic body was the essence and point of the Kennecott Corp. specification. This is significantly different than the current case where not only is the "monolayer solid surface" not the focus of the claimed invention, but the 96 well microtiter plate coated with streptavidin is not the only solid support which falls within the scope of the claim. In Kennecott Corp., the claim was limited to a specific sintered ceramic body, with "at least 95% by weight of the silicon carbide is of the alpha phase" Kennecott Corp. at 1196. That structural limitation of the silicon carbide being of the alpha phase is what provided the structure necessary to support the inherent "equiaxed microstructure". The current claims lack any specific structure corresponding to the relied upon portion of the specification and are not limited to any particular solid support. The current claims encompass beads, nitrocellulose paper, nylon, slides, silicon chips and any other support used in the art. There is no evidence of record that all of these

structures will inherently result in formation of a monolayer. Therefore, the current situation is significantly different than Kennecott Corp. because there is no structure in the claim which inherently must perform the function of having a monolayer and there is no structure in the specification which must inherently be a monolayer.

This is consonant with the other cases on new matter. The CCPA decision in In re Reynolds, 170 USPQ 94 (CCPA 1971) also deals with whether a limitation is inherently supported by the specification. In Reynolds, the CCPA found that a figure in the specification showed the element necessary to provide inherent support for the claim. This is also distinguished from the current case, where there is no showing in the specification of any specific device which has a monolayer. Again, the essence and point of the Reynolds application was VHF-UHF tuner and there was a specific drawing, figure 2, in the specification which supported the claim limitation by directly showing the inherent property. This is significantly different than the current case where no drawing showing a monolayer, no discussion of a monolayer and no device which had a monolayer were specifically referenced in the specification.

Also in accord is In re Ruschig, 154 USPQ 118, 123 (CCPA 1967), which notes "Is the compound of claim 13 described therein? Does the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound? Having considered the specification in the light that has been shed on it by all the arguments pro and con, we conclude that it does not." The same question, addressed in the current context, would be "Is the monolayer of claim 1 described therein? Does the specification convey clearly to those skilled in

the art, to whom it is addressed, in any way, the information that appellants invented a method using a monolayer?" A review of the specification would inevitably lead to the conclusion that there is no support for the position that the specification "clearly conveys" the invention of the use of a monolayer.

Therefore, the decisional law of the Federal Circuit and CCPA support the conclusion that the term "monolayer" is new matter in the current claims.

(b) The Evidence as a whole does not support the conclusion that a "monolayer" is an "inherent property" of a solid surface

Appellant argues that the evidence was not considered by the examiner. In fact, all of the evidence was carefully considered but was not found to be sufficient to support the conclusion which Appellant wishes to draw, that a "monolayer" is an inherent property of DNA attached to any solid surface. There is no question that Dr. Strohner expressly states that "immobilization of streptavidin onto solid surfaces (such as plastic microtiter plates and membranes) will result in a reactive streptavidin monolayer (see Declaration of Dr. Strohner)." However, the other evidence presented by Appellant, as well as the Jordan paper, rebut the conclusion that "monolayers" are inevitable and inherent.

At the first page of Appellant's Exhibit 4 (page 57 in eDAN of the appeal brief document), the document states "As opposed to multilayers of streptavidin, a monolayer does not introduce the risk of streptavidin being sterically hidden and un-available for binding of your ligand/target." This is an express statement that a monolayer is not inevitable and will not necessarily result, since otherwise the document would not

mention multilayers at all. It is clear from this Dynal corporation webpage that multilayers of streptavidin are a problem in their device and that some devices may have such multilayers. This directly contradicts Appellants argument that the plates "available from manufacturers" (the only support for the proposition that monolayers are inherent in the specification) inherently comprise monolayers.

The second subpart of Exhibit 4 teaches away from the use to which Appellant would wish to put it, since the current claims prefer measurement of the fluorescent dye SYBR Green and the Promega catalog specifically states "The use of fluorescence for detection of captured molecules is not recommended at this time (see page 1 of Promega catalog, page 58 in eDAN of the appeal brief document)." This teaching away from Appellants actual invention by the exhibit renders the "inherent property" argument untenable since the manufacturer from which this device is unavailable teaches not to use the device in Appellant's method. Consequently, it would not be "inherent" to use the device in Appellant's method.

The Perkin-Elmer, Nunc, Upstate product and Roche plates provide no discussion regarding whether there is a monolayer or not on the plate and therefore do not directly inform this analysis. When Appellant states that no rebuttal was made of whether these are monolayers, no rebuttal is necessary. There is no evidence either way. In fact, the Roche catalog's teaching of two different amounts of biotin binding at page 5 of the catalog (page 73 in eDAN of the appeal brief document) is suggestive, however, that both the regular and "high bind" plates cannot be composed of monolayers. That is, if the high bind is capable of binding four times as much biotin as

the regular plates, the structure of the two streptavidin devices would seem likely to be different, so that both plates cannot both be monolayers. In any case, it is clear that none of these four plates provides any direct discussion of monolayers whatsoever and provide no evidence that the streptavidin on the plates is in a monolayer form.

The Strohner declaration was given some weight. However, this declaration provides no evidence supporting the assertion that monolayers are inevitable and simply represents the opinion of Dr. Strohner. This opinion is directly rebutted by the Jordan reference.

Jordan expressly teaches that DNA hybridization onto surfaces with streptavidin can form multilayers. Appellant ignores the plain statement of Jordan that "The SPR signal resulted from hybridization onto immobilized probes is further amplified by the formation of streptavidin/DNA multilayers which grow by a combination of DNA hybridization and biotin-streptavidin binding (see abstract of Jordan)." **A multilayer is not a monolayer**. Jordan further cites other art which notes multilayer formation, stating "Caruso et al have shown that multilayer formation will occur via the successive deposition of avidin and poly(sytrenesulfonate) and that once these multilayers are formed it is possible to bind a biotin labeled oligonucleotide to the avidin in these multilayers and subsequently hybridize another oligonucleotide to this immobilized DNA (see page 4946, last sentence to page 4947, first sentence)." Jordan further notes that "These colloidal gold particles aggregate in a single solution, suggesting that perhaps streptavidin/DNA multilayers at gold surfaces could also be formed from a single adsorption solution (see page 4947, column 1)."

Therefore, the decisional law of the CCPA and Federal circuit, and the evidence of record, both Exhibits 1 and 2 of Appellant and the Jordan reference, all of which either teach multilayers or teach away from Appellant's method, as well as the absence of any ipsis verbis support, when weighed against the Strohner declaration, support the conclusion that there is a prima facie case of lack of descriptive support for the added limitation of "monolayer" as an inherent property of the specification.

Priority

Appellant then argues the priority issue. The arguments are the same as above. However, this issue is not particularly relevant to the prior art rejections, which all rely upon art which antedates the priority documents and do not depend upon this issue.

Issue 2 – Prior art rejections

Prima facie case

The basic prima facie case of obviousness in this application is based upon the combination of Stimpson and Wittwer. Stimpson teaches a method of detecting DNA variation by monitoring the formation or dissociation of a complex consisting of a single strand of a DNA sequence and an oligonucleotide specific for the single stranded DNA sequence specific for one allele of the variation and capable of hybridizing to the single strand (a) to form a duplex and a marker detection of the duplex structure of (a) plus (b) which forms a complex with the said duplex which method comprises steadily and progressively adjusting the temperature by 1°C increments, continually measuring an output signal indicative of the duplex formed from the strand (a) and probe (b) (see page 6382, figure 3) and recording the conditions at which a

change in reaction output signal occurs which is attributable to formation or dissociation of the complex and is thereby correlated with the strength with which the probe (b) has hybridized to the single strand (a). The only element missing from the Stimpson reference is the use of an intercalating dye as the marker. Wittwer teaches a similar method in solution phase using the double stranded DNA intercalating dye, SYBR green I.

While the Appellant disputes the prima facie case of obviousness, the Appellant does not dispute that Stimpson and Wittwer teach the steps as illustrated in the rejection. What Appellant does dispute is whether there is motivation to modify Stimpson as suggested by Wittwer and whether the combination would have a reasonable expectation of success in yielding the claimed invention. The conclusion of prima facie obviousness of the claims over Stimpson and Wittwer (and Heller and Konrad for dependent claims) is supported by several distinct lines of reasoning, including the express motivation taught by Wittwer, the reasonable expectation of success and the scope of the claims as properly interpreted.

In particular regarding the term "monolayer", to the extent that Appellant's invention uses a "monolayer", it is untraversed by Appellant that the Stimpson reference uses a DNA chip that necessarily comprises a "monolayer".

Appellant provides no evidence for any secondary considerations with regard to the claims. Consequently, the issue is solely whether there is a prima facie case of obviousness.

Motivation

Appellant argues that there is no motivation to combine the Wittwer method, in which SYBR Green is used to monitor PCR amplification, with the Stimpson method of monitoring DNA variation on a solid support.

This is incorrect. There is specific motivation which is provided in the rejection. In particular Wittwer states "SYBR™ Green I is a preferred double strand specific dye for fluorescence monitoring of PCR, primarily because of superior sensitivity, arising from greater discrimination between double stranded and single stranded nucleic acid. SYBR™ Green I can be used in any amplification and is inexpensive. In addition, product specificity can be obtained by analysis of melting curves, as will be described momentarily (column 23, lines 9-16)". Therefore, when the ordinary practitioner looks at the motivation from Stimpson and Wittwer, there is clear motivation to detect using SYBR Green I.

When Appellant then argues that Wittwer does not recognize the use of SYBR green in analyzing DNA which shares some sequence similarity but has some level of variation, this argument is factually incorrect. Wittwer, at column 42, example 20, expressly discusses the use of SYBR green for monitoring reactions with competitors which have the same priming sites but differ in length. This is precisely the same type of assay as that in which Stimpson was interested, an assay in which sequences with some common structure and some different structure are distinguished. Therefore, Wittwer provides an express teaching to analyze DNA variation using SYBR Green in example 20.

While Appellant is correct that Stimpson prefers not to use fluorescent dyes, Stimpson does not address DNA intercalators at all and specifically does not address the DNA intercalator SYBR Green. The reason Stimpson gives for not preferring fluorescent dyes is that low signal intensity requires a longer scanning time (see page 6379, column 2). This is not a teaching away from the use of fluorophores, much less SYBR Green which has superior sensitivity according to Wittwer. As MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Stimpson had a preferred embodiment, this embodiment does not prevent the use of alternative embodiments or constitute a teaching away from the use of SYBR Green as taught by Wittwer.

. Appellant's argument that a different system would be necessary to combine Stimpson and Wittwer is also incorrect. Wittwer expressly teaches the fluorescent devices necessary to detect the SYBR green dye. The same CCD device used by Stimpson for wave guide detection would detect SYBR Green fluorescence. The only different requirement would be a different light source.

Appellant then argues that SYBR Green lacks the sensitivity required for detection on a solid support because Wittwer does not see a signal until about 20 rounds of amplification. Appellant here does not provide any evidence to support this

point, but simply argues the sensitivity issue. One way of analyzing this methodically is to determine how many molecules of DNA are necessary for Wittwer to detect using SYBR green in the PCR reaction relative to how many molecules of DNA are present on the waveguide of Stimpson. In order to give Appellant the benefit of all doubt, it will be assumed that the PCR of Wittwer doubles fully in every round of amplification (which is certainly an overestimate). In that case, the doubling would be 2^{20} times the number of starting molecules, which Wittwer indicates is about 15,000 (see column 33, line 59). Wittwer therefore demonstrates detection of 15,728,640,000 or 1.5×10^{10} molecules of DNA. Stimpson teaches at page 6380 that the oligonucleotides were diluted to 50 ug/ml and 1 ul drops were dried on the slides. 50 ug/ml is the same as 50 ng/ul so a 1 ul drop of oligonucleotide would have 50 nanograms of the oligonucleotide. The first oligonucleotide, TATCATCTTTGGTGT has a molecular weight of 4564.1 g/mol. That molecular weight is equivalent to 4564×10^9 ng/mol. 50 nanograms divided by 4564×10^9 ng/mol yields 1.09×10^{-11} moles of oligonucleotide in the 1 ul drop that was dried on the slide. Multiplying the number of moles by Avogadro's number (6.02×10^{23} molecules/mol) yields 6,595,092,024,539 or 6.6×10^{12} molecules of DNA in the 1 ul drop.

The above calculation shows that there is 100 times as many molecules of nucleic acid on the array of Stimpson as would be found in the PCR reaction mixture of Wittwer at 20 cycles. Therefore, Wittwer shows that the SYBR Green detection method may be as much as 100 times more sensitive than the Stimpson method. Not only

would this motivate the ordinary practitioner, but if sensitivity of detection is the issue, SYBR Green clearly has a more sensitive detection capacity.

Consequently, there can be no greater motivation than the detailed encomium provided by Wittwer, which represents a paean to the excellence of SYBR Green I in detection of nucleic acids. Such a statement clearly motivates the use of SYBR Green I in any amplification based assay to the ordinary practitioner

Reasonable expectation of Success

With regard to Appellant's argument that there was no reasonable expectation of success to combine the Wittwer and Stimpson references, this requirement is derived from the caselaw. The Federal Circuit in In re O'Farrell, 853 F.2d 894, 903, 904 (Fed. Cir. 1988) noted

> "The admonition that "obvious to try" is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. (citations omitted). In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (citations omitted). Neither of these situations applies here."

Following the analysis of In re O'Farrell, This is not an instance where the prior art references of Wittwer and Stimpson suggest varying a variety of parameters. Here, Wittwer precisely, definitely and clearly suggests and motivates the use of SYBR Green

I. Thus Wittwer expressly shows the expectation of success in using SYBR Green I for detection of DNA in amplification based assays. So there is specific guidance and a nearly 100% expectation of success, since Wittwer clearly demonstrates that SYBR Green I can be used with great success. With regard to the issue of general guidance, both Wittwer and Stimpson give specific guidance as already noted to combine their methods. Thus, as in O'Farrell, neither of the "obvious to try" situations occurs here, since there is specific and direct teaching of the parameters of the invention with specific guidance to select SYBR Green I. Appellant continues by arguing incorrectly that the combination would not represent the invention, based upon the sensitivity issue for the reasons discussed above. Based upon the data, Wittwer's SYBR Green is more sensitive, by a factor of 100, than Stimpson's wave guide, which represents a clear desire to make the invention.

Appellant then argues that the claim limitation to 40 basepairs is not rendered obvious by either Wittwer or Stimpson in combination. This is incorrect for several reasons. First, Wittwer expressly teaches an 81 basepair cystic fibrosis gene product (column 40, lines 58-67), which is more than 40 basepairs. Second, when Wittwer suggests detection of the Factor V Leiden gene, Wittwer suggests probes of 15-40 nucleotides in length (see column 44, lines 3-4). Third, while Stimpson exemplifies 15 mer oligonucleotides, simply increasing the length of the oligonucleotide is a prima facie obvious variation of Stimpson's length in view of Wittwer's teaching that probes can be 15-40 nucleotides in length. Therefore, there is express teaching of lengths of at least 40 basepairs, and this element is met by the prior art of Wittwer and Stimpson.

Scope of the Claims

Appellant next argues that Baldeschwieler and Kwok Declarations support the conclusion that "a skilled person in the field would not have been motivated to replace the signal generation mechanism described in Stimpson et al with any kind of fluorescent system (see Baldeschwieler declaration)". The Kwok declaration is not drawn to the current rejection, but is drawn to the previous rejection (overcome by the use of the term "monolayer") in which Drobyshev is the primary reference. However, Kwok argues that the liquid phase method of Wittwer would not be expected to function on a solid phase.

To the extent that these declarations represent the opinion of the Declarant's, they are given some weight. However, a declaration is most persuasive when it presents evidence, not opinion or argument, which evidence addresses the elements of the prima facie case. The only evidence cited in the Baldeschwieler declaration is in the paragraph numbered 2, where Dr. Baldeschwieler states "one skilled in the art would not expect the DNA binding capacity of any of the stable and common 2-D surfaces and chemistries to yield sufficiently strong fluorescent signals sufficiently 'instantly' (sub-second) in a fluorescence based assay method to allow for dynamic tracking of signal changes in real-time, when applying practically useful rates of heating." This Declaration is rebutted in two ways. First, as discussed in the motivation section above, the calculated sensitivity of SYBR Green I is 100 times that of the waveguide of Stimpson, and Dr. Baldeschwieler's opinion is not based on the specific sensitivity of

SYBR Green I, but on other fluorophores with lesser sensitivities. Therefore, the opinion is not directed towards the rejection at hand.

Second, and perhaps more importantly, the claim permits the adjustment of temperature at a rate of 0.01 degree per second, therefore taking 100 seconds or 1 minute 40 seconds to increase the temperature one degree. Even Stimpson recognizes that a 1 minute scanning time can function, though it may be longer than optimal (see page 6379, column 2). Therefore, when Dr. Baldeschwieler states that "subsecond" signal detection is required, this is INCORRECT. The claim does not require subsecond signal detection and has no rate of measurement required whatsoever, other than "continuous". Therefore, to the extent that Dr. Baldeschwieler relies upon evidence and not opinion to overcome the rejection, this evidence is not related to the limitations of the invention as claimed.

The Kwok Declaration is entirely an opinion reference without any evidence whatsoever to support the opinion. In view of the strong motivation by Wittwer to use SYBR Green in analytical methods, weighed against the declarations of Dr. Kwok and Dr. Baldeschwieler, the conclusion based upon the evidence is that the prima facie case of obviousness should be maintained.

103 Rejections with Heller and Konrad

With regard to Appellant's arguments on the 103 rejections which use Heller and Konrad, Appellant relies upon overcoming the basic prima facie case of obviousness of Stimpson in view of Wittwer. The same arguments given above apply to the arguments with regard to these further 103 rejections.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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